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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/931,795	08/16/2001	Rima Rozen	04844/005005	3757

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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/931,795	ROZEN, RIMA	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the amendment filed July 24, 2003. Claims 29-55 are pending. Applicants arguments and amendments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (i) methods for identifying individuals in need of therapy for schizophrenia by detecting the presence of a C to T mutation at position 677 of the MTHFR gene, (ii) methods of identifying individuals with schizophrenia that have an increased likelihood of responding to neuroleptic therapy by detecting individuals who are homozygous for the T allele at position 677 of the MTHFR gene and (iii) methods of treating individuals for schizophrenia by detecting the presence of a C to T mutation at position 677 of the MTHFR gene and administering to those patients that are homozygous for the T allele a neuroleptic medication, does not reasonably provide enablement for methods of selecting a therapy for a subject suffering from any type of psychosis wherein the methods detect any mutation in the MTHFR gene or for research methods which determine whether a mutant MTHFR allele is associated with the safety or efficacy of a type of treatment for psychosis. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The claims as amended are drawn to methods for selecting a safe and/or efficacious therapy for a subject suffering from schizophrenia wherein said methods comprise analyzing the MTHFR nucleic acid in a sample from said subject and detecting the presence of a heterozygous C/T mutation at position 677 MTHFR mutant allele in said subject as indicative of the safety or efficacy of treatment. The claims further include methods of determining whether a heterozygous C/T 677 MTHFR allele is associated with the safety or efficacy of a treatment for schizophrenia and methods of preventing, delaying or treating schizophrenia by detecting a heterozygous C/T 677 MTHFR allele and determining a preferred therapy. The claims recite that it is further determined that the individual has a second MTHFR mutation. The claims fail to state how the step of determining the second MTHFR mutation or the knowledge that the individual has a second MTHFR mutation is related to the claims in terms of influencing the selection of therapy. The specification (page 22) indicates that the presence of a MTHFR mutant allele may be used to evaluate any therapy for schizophrenia in terms of

its safety, efficacy (i.e., ability to ablate, reduce or stabilize symptoms or prevent the onset of symptoms in subjects at risk of the psychotic disorder) or toxicity (e.g., reduced pharmacological or physiological effects).

However, the claims are not commensurate in scope with the enabling disclosure because, while the specification teaches an association between homozygosity for the 677T allele and responsiveness to neuroleptic therapy in schizophrenic patients, the specification has not adequately taught one of skill in the art how to predictably select any type of safe or effective therapy for schizophrenia by detecting an individual heterozygous for a C/T allele at position 677 of the MTHFR gene. In particular, the specification (see, for example, table 2) discloses several missense and splice site mutations in the MTHFR gene which result in decreased activity and/or decreased thermal stability of the encoded MTHFR protein. The specification also teaches that a block in methyltetrahydrofolate leads to elevated homocysteine levels and that high plasma levels of homocysteine may be a risk factor for some types of pathological conditions, including mental retardation, seizures and psychiatric disturbances. Data is provided in the specification showing that the homozygous and heterozygous C677T mutations were found more frequently in schizophrenia patients than in controls (pages 79-82). The specification also teaches that schizophrenic patients homozygous for the 677T allele are more likely to respond to neuroleptic treatment (see page 82 and Table 9). However, the specification does not teach or provide sufficient guidance to identify additional mutations in the MTHFR gene that are associated with response to treatments for subjects having schizophrenia. The teachings in the art indicate the

unpredictability in establishing a correlation between a MTHFR allele and disease. For example, Zuliani (Acta Neurol Scand (2001) 103: 304-308) states that while subjects with the MTHFR C677T mutant allele have moderately increased plasma homocysteine levels, the C677T mutation has not been found to be associated with AD, cognitive impairment, or vascular dementia (see page 306). Gussekloo et al (Journal of Neurology, Neurosurgery, and Psychiatry (1999) 67: 535-538) also teaches that the MTHFR C677T mutation is not correlated with dementia in persons 85 years and over. Chapman (Stroke (1998) 29: 1401-1404; cited in the IDS of August 16, 2001) also reports that the MTHFR C677T mutation is not associated with vascular dementia or Alzheimer's disease. The ability to establish a correlation between a mutation and a response to therapy is highly unpredictable, even in circumstances in which the effect of the mutation (e.g., decreased enzyme activity or thermostability) has been determined. Furthermore, the specification is also not enabling for methods which detect any mutation other than the C677T mutation as indicative of response to treatment for schizophrenia. The specification teaches "disease causing" mutations in the MTHFR gene can be identified by detecting those mutations which result in decreased activity of the encoded MTHFR protein. The specification does not teach any other types of mutations which are "indicative of MTHFR deficiency". It is highly unpredictable as to what other types of alterations in the MTHFR gene would be associated with psychosis or schizophrenia and could be used to select treatment for psychosis or schizophrenia. No specific guidance is provided in the specification as to how to predictably identify additional mutations in the MTHFR gene which could be used to diagnose psychosis or

schizophrenia. In fact, the teachings of the specification suggest that benign polymorphisms are not associated with disease and therefore could not be used to predict a patients response to treatment. For example, the specification which teaches that the T1317C allele is likely a benign change. Accordingly, it does not appear that benign polymorphisms, particularly the T1317C polymorphism, could be used to select therapy for any type of psychosis or for schizophrenia.

As discussed above, the claims are inclusive of methods of identifying therapies that can be used to delay or prevent the onset of psychosis. The specification (page 58) indicates that individuals that are homozygous for the C677T mutation may benefit from folic acid supplementation. As discussed in the specification, higher levels of plasma folate may lead to normalization of homocysteine levels in individuals having this MTHFR mutation and may prevent the occurrence of disorders associated with high levels of homocysteine. However, the specification has not established that any type of therapy could be used to delay/prevent the onset of schizophrenia or psychosis. The specification has disclosed only that individuals that are homozygous for the 677T allele are more likely to be responsive to neuroleptic treatment. The specification does not identify any alleles that are associated with toxicity or safety of therapy and it is also highly unpredictable as to how the presence of 677T allele or any other MTHFR allele could be associated with toxicity and safety of therapy. It is highly unpredictable as to how a mutation in a gene will effect drug responsiveness in general. The specification provides no guidance as to how to identify additional types of drug responsiveness which are associated with MTHFR mutations.

With respect to claims 37-44, the specification is not enabling for methods of determining whether a MTHFR allele is associated with response to therapy. Such methods constitute research methods in which the sole purpose of the method is to evaluate a MTHFR allele and determine whether such an allele is correlated with the safety or efficacy of some type of therapy. It is highly unpredictable as to which alleles in the MTHFR gene would be correlated with response to therapy. The showing of one allele that is associated with response to neuroleptic medications in patients with schizophrenia is not commensurate in scope with the breadth of the claims which analyze any allele of the MTHFR gene and try to determine if one or more of these alleles is associated with responsiveness to therapy in any patient having psychosis.

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the state of the art indicates that only the homozygosity for the 677T MTHFR allele is correlated with responsiveness of

schizophrenia patients to neuroleptic treatment. Furthermore, the state of the art indicates that in general it is highly unpredictable as to how a particular mutation will effect drug responsiveness unless there is a specific correlation between the effect of the mutation and the activity of the drug. In the absence of a specific correlation between a mutation and drug activity, mutations which are correlated with drug responsiveness can only be identified by randomly searching the MTHFR gene for genetic alterations and trying to determine whether these mutations alter the responsiveness or toxicity to any drug. Such random, trial by error experimentation is considered to be undue. Accordingly, in view of the high level of unpredictability in the art and the lack of information and guidance provided in the specification regarding an association between schizophrenia and other MTHFR mutations and regarding MTHFR mutations and response to any therapy in a patient having schizophrenia, undue experimentation would be required to practice the invention as it is broadly claimed.

3. **RESPONSE TO ARGUMENTS:**

In the response of July 24, 2003, Applicants state that because they have shown that individuals heterozygous for the C/T 677 MTHFR mutation are correlated with schizophrenia, the specification has enabled methods for selecting a safe or efficacious therapy for a subject with schizophrenia based on the presence of a heterozygous C/T 677 MTHFR mutation.

Applicants arguments have been fully considered but are not persuasive. It is agreed that Applicant's have established that heterozygosity for the C/T 677 MTHFR mutation is associated with the occurrence of schizophrenia. Thereby, Applicants have

enabled methods for detecting an increased likelihood of developing schizophrenia by detecting the presence of heterozygosity for the C/T 677 MTHFR mutation. However, the correlation between the 677 C/T allele and schizophrenia does lead one to methods for determining whether any therapy given to a patient with schizophrenia will be safe or effective. As discussed in the above rejection, Applicants have shown only that schizophrenic patients **homozygous** for the 677T allele are more likely to respond to neuroleptic treatment (see page 82 and Table 9). There is no information provided in the specification to establish that individuals heterozygous for the 677 mutation are more likely to respond to neuroleptic treatment. Applicants have argued that while the prior art taught an association between homozygosity of the 677T allele and schizophrenia, these findings would not lead one to conclude that individuals heterozygous for the 677C/T allele are also at an increased risk of developing schizophrenia. This same unpredictability extends to establishing whether there is an association between heterozygosity at the 677T/C and response to therapy. Accordingly, the results set forth in the specification regarding an association between response to neuroleptic treatment in individuals homozygous for 677T cannot be used to establish that individuals heterozygous for 677T/C are also more likely to respond to neuroleptic treatment. Further, the specification does not teach an association between response to any other therapies given to schizophrenic patients and the presence of the 677 mutation or any other second MTHFR mutation. The claims include patients with more than one MTHFR mutation. Yet, there are no teachings in the specification as to how the presence of a second MTHFR mutation influences response to therapy. The

claims do not clearly state how the information of determining that an individual is heterozygous for the 677 MTHFR allele or has a second MTHFR mutant allele is used to determine the safety or efficacy of a therapy. The claims merely state that one determines the presence of a C/T mutation at position 677 of MTHFR "wherein the presence of said mutation is indicative of the safety or efficacy of a therapy." This statement infers that any therapy would be safe and effective for an individual as long as they are heterozygous for the 677 mutation. The claims do not clarify how one uses the information regarding the presence of heterozygosity at the 677 allele to determine that a therapy is safe or effective and to then select a safe or effective therapy. The claims also include selecting therapies for the schizophrenic patient that are not related to treatment of schizophrenia directly since the claims do not set for the type of therapy that is being selected.

Additionally, Applicants response does not address the rejection as it pertains to the fact that claims 37-44 constitute a research method in which the sole purpose of the method is to evaluate a MTHFR allele and determine whether such an allele is correlated with the safety or efficacy of some type of therapy. Furthermore, the response and amendments do not address the rejection as it pertains to the fact that the specification has not taught methods for preventing or delaying treatment of schizophrenia. Again, there are no teachings in the specification of any particular methods for preventing or delaying the onset of schizophrenia and an association has not been established between preventing or delaying schizophrenia and the occurrence of heterozygosity at the 677 MTHFR allele.

The following are new grounds of rejection necessitated by Applicants amendments to the claims:

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34-44, 50-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 34-35, 42-44 and 50-52 are indefinite over the recitation of "subject is determined to comprise at least two MTHFR mutations" because it is not clear as to what is intended to be meant by the fact that the subjects are determined to comprise 2 mutations. It is not clear as to whether this is a known, inherent property of the nucleic acids or whether the method includes an actual step of analyzing for the presence of at least 2 mutations in the MTHFR gene and determining a therapy based on the presence of the stated 2 mutations. It is unclear as to how the limitation that the nucleic acid has 2 mutations relates to the remainder of the claim. Is the second mutation used for determining the therapy? If the second mutation is not present, is the selection of therapy different? In these claims, are methods for selecting a therapy only to be performed on individuals that have both of the mutations? The claims do not clarify the relevance of the recitation of "subjected is determined to comprise at least two MTHFR mutations" to the method of selecting a safe and/or efficacious therapy.

B. Claims 37-44 are indefinite over the recitation of "said response" because this phrase lacks proper antecedent basis since the claim as amended does not previously refer to a response.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers
November 13, 2003

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER